ChemComm

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Cite this: *Chem. Commun.*, 2013, **49**, 11797

Received 20th September 2013,
Accepted 25th October 2013

DOI: 10.1039/c3cc47197g

www.rsc.org/chemcomm

One pot synthesis of bioactive benzopyranones through palladium-catalyzed C–H activation and CO insertion into 2-arylphenols†

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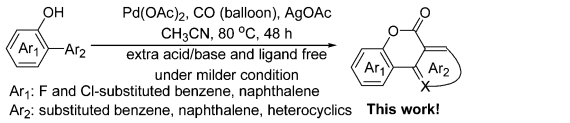
Palladium-catalyzed oxidative carbonylation of 2-arylphenols through C–H bond activation and C–C and C–O bond formation under acid–base free and mild conditions has been developed. The reaction tolerates a variety of substrates and provides biologically important benzopyranone derivatives in up to 87% isolated yield.

The methodology of transition-metal-catalyzed C–H bond activation has evolved as a powerful tool for covalent C–X bond formation (X = C, N, O) with features of step-economy and green chemistry primarily because halogenated materials are not required as starting substrates. Many of these reactions have been extensively used for the syntheses of various natural products and bioactive molecules.[1] In this scope, metal-catalyzed carbonylation of organic compounds in the presence of carbon monoxide in combination with C–H bond activation has become an important tool for C–C and C–X bond-forming processes.[2] Yu *et al.* have recently demonstrated the *ortho*-carbonylation of anilides and carboxylic acids through Pd(II)-catalyzed C–H bond activation under a CO atmosphere.[3] Other recent reports also revealed the synthesis of phthalimides[4] through tandem C–H bond activation and carbonylation of benzamides catalyzed by palladium, ruthenium or rhodium complexes. Similarly, Lei *et al.* achieved Pd-catalyzed oxidative dual C–H functionalization–carbonylation of diaryl ethers for the synthesis of xanthones.[5] In addition to the C–H activation–functionalization on the same aryl ring as the directing group, the metal-catalyzed C–H activation of neighbouring aryl rings, the 2-directing group substituted biaryl systems, has also emerged for the syntheses of fluorenones,[6] carbazoles,[7] dibenzofurans[8] and phenanthridinones.[9] We recently reported the annulation of *N*-sulfonyl-2-aminobiaryls with [60]fullerenes through palladium(II)-catalyzed C–H bond activation to afford n-type materials, [60]fulleroazepines.[10] In this system, we have also succeeded in the preparation of phenanthridinones through Pd-catalyzed oxidative CO insertion into *N*-sulfonyl-2-aminobiaryls under acid-free conditions.[11] Due to their importance in biological and materials science fields,[12] the syntheses of benzopyranones have received substantial attention. Previous approaches relied on multistep procedures for [3+3] cyclization of silyl enol ethers with 3-silyloxy-2-en-1-ones,[13] oxidation of 6*H*-benzo[*c*]chromene,[14] Cu(I)-mediated cyclization of 2-halobiarylcarboxylic acid,[15] Suzuki–Miyaura cross-coupling of *o*-bromoarylcarboxylates and *o*-hydroxyarylboronic acids,[16] and Pd-catalyzed CO insertion into 10-hydroxy-10,9-boroxarophenanthrenes.[17] Very recently, Inamoto *et al.*[18] and Shi *et al.*[19] independently demonstrated ruthenium and palladium-catalyzed CO insertion into 2-arylphenols *via* C–H activation. These related reports utilized conditions with bases (K_2CO_3 or Cs_2CO_3 or Na_2CO_3) or carbene ligands (IPr) as additives in mesitylene at >100 °C.[8a] Our continuing interest in the C–H activation reactions of 2-substituted biaryls relevant to our developed fulleroazepines and phenanthridinone syntheses[10,11] prompts us to scrutinize the reaction conditions for the syntheses of benzopyranones from 2-arylphenols by Pd-catalysis. Herein we report the oxidative insertion of carbon monoxide into 2-arylphenols through C–H bond activation without extra addition of acid, base or ligand at lower reaction temperature (Scheme 1).

We optimized the studied carbonylation reaction using biphenyl-2-ol (**1a**) as a model substrate and summarized the results in Table 1. We started with previously successful conditions with 10 mol% of $Pd(OAc)_2$ and silver acetate as oxidants in anhydrous CH_3CN for carbonylation of **1a** and observed the formation of 6*H*-benzo[*c*]chromen-6-one (**2a**) in 37% isolated yield (entry 1). The catalytic reaction in other solvents such as DMF, toluene, DMSO, THF or butyronitrile gave lower product yields than that in CH_3CN (entries 2–6). We noted that reactions



Scheme 1 Palladium-catalyzed C–H bond activation–carbonylation of 2-arylphenols for syntheses of benzopyranones.

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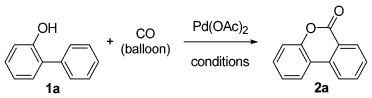
† Electronic supplementary information (ESI) available. CCDC 949418 and 951032. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc47197g

Table 1 Optimization of reaction conditions[a]



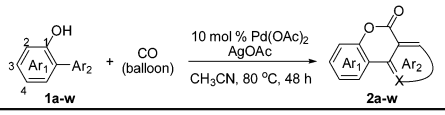
Entry	Oxidant (equiv.)	Additive	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	AgOAc (2)	—	CH_3CN	80	24	37
2	AgOAc (2)	—	DMF	80	24	23
3	AgOAc (2)	—	Toluene	80	24	11
4	AgOAc (2)	—	DMSO	80	24	Trace
5	AgOAc (2)	—	THF	80	24	28
6	AgOAc (3)	—	Pr-CN	110	24	31
7	Ag_2O (2)	—	CH_3CN	80	24	35
8	Ag_2CO_3 (2)	—	CH_3CN	80	24	25
9	$KHSO_5$ (2)	—	CH_3CN	80	24	24
10	$K_2S_2O_8$ (2)	—	CH_3CN	80	24	33
11	$Cu(OAc)_2$ (2)	—	CH_3CN	80	24	36
12	BQ (2)	—	CH_3CN	80	24	28
13	AgOAc (3)	—	CH_3CN	80	24	50
14	AgOAc (4)	—	CH_3CN	80	24	42
15	**AgOAc (3)**	—	**CH_3CN**	**80**	**48**	**68**
16	AgOAc (3)	—	CH_3CN	80	72	60
17	AgOAc (3)	—	CH_3CN	80	96	49
18	AgOAc (3)	NaOAc (1)	CH_3CN	80	24	27
19	AgOAc (3)	KOAc (1)	CH_3CN	80	24	29
20	AgOAc (3)	2,4,6-Collidine	CH_3CN	80	48	59
21	AgOAc (3)	TFA (5)	CH_3CN	80	24	—
22	AgOAc (3)	AcOH (2)	CH_3CN	80	24	40
23[c]	AgOAc (3)	—	CH_3CN	80	48	47
24[d]	AgOAc (3)	—	CH_3CN	80	48	38
25[e]	AgOAc (3)	—	CH_3CN	80	48	46

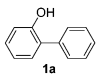
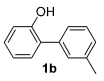
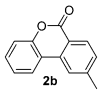
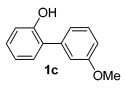
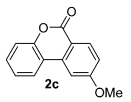
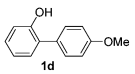
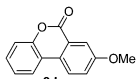
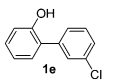
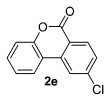
[a] All the reactions were performed with **1a** (50 mg, 0.29 mmol), 10 mol% of $Pd(OAc)_2$ (6.6 mg, 0.029 mmol) under CO in freshly distilled solvents (4 mL) unless otherwise noted. [b] Isolated yields. [c] 15 mol% of $Pd(OAc)_2$ was employed. [d] $PdCl_2(PPh_3)_2$ was used as a catalyst. [e] Reaction was carried out with undistilled CH_3CN.

with Ag_2O, $K_2S_2O_8$ and $Cu(OAc)_2$ as oxidants produced comparable yields to that with AgOAc (entries 7–12) and concluded that AgOAc and $Cu(OAc)_2$ can be suitable oxidants in CH_3CN. This notion is quite different to our previously studied carbonylation of *N*-sulfonyl-2-aminobiaryls since it only worked better with AgOAc.[11] We further investigated the relative stoichiometric amounts of reactants and reaction time for achieving optimal yields. The reaction with a higher amount of silver acetate (3 and 4 equiv.) provided **2a** in 50% and 42% yields (entries 13 and 14) and those with prolonged reaction times of 48, 72 and 96 h gave 68, 60 and 49% yields, respectively (entries 15–17). The demand for a longer reaction time than 24 h is likely due to the slow C–O reductive elimination process.[8a] Our naïve thought to use bases as additives to quench the slightly acidic conditions, such as using NaOAc, KOAc and 2,4,6-collidine, did not improve the yields (entries 18–20). Neither the explored reaction took place under more acidic conditions with extra acidic additives such as TFA or AcOH (entries 21 and 22). The above observation is consistent with Liu's conclusion that the phenol moiety behaved as a neutral σ-donor.[8a] We further found that an increase of the catalyst loading and replacement of the catalyst with $PdCl_2(PPh_3)_2$ did not help (entries 23 and 24). Our control experiment showed that the reaction conditions have to be anhydrous since the use of non-distilled acetonitrile only gave 46% yield (entry 25).

Under the standard reaction conditions (Table 1, entry 14), substrates **1b–d** without substituents on the Ar_1 ring and with an electron-donating group (EDG), methyl or methoxy moiety, on the

Table 2 Palladium-catalyzed synthesis of benzopyranone derivatives[a]



Entry	Substrate **1**	Product **2**	Yield[b] (%)
1			68
2			70
3			85
4			87
5			77
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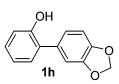
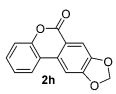
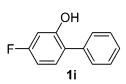
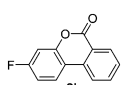
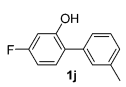
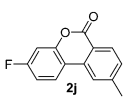
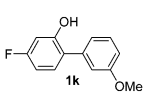
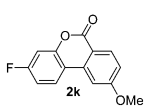
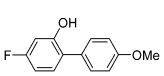
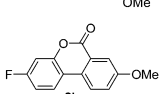
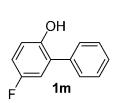
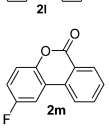
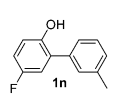
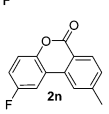
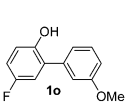
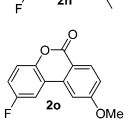
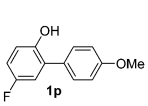
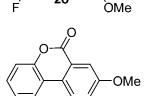
8			68
9			65
10			72
11			87
12			74
13			78
14			75
15			81
16			86

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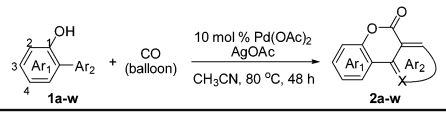
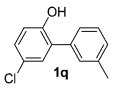
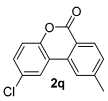
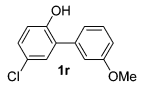
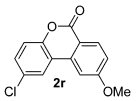
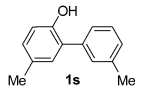
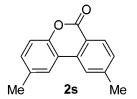
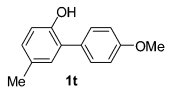
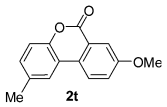
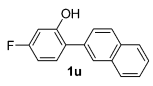
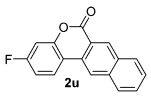
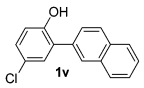
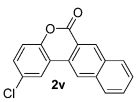
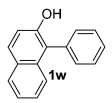
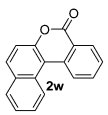
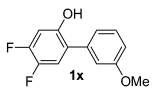
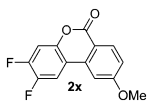
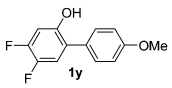
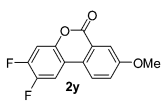


Entry	Substrate **1**	Product **2**	Yield[b] (%)
17			75
18			85
19			—
20			—
21			72
22			74
23			75
24			—
25			—

[a] All reactions were carried out with substrate **1** (50 mg), $Pd(OAc)_2$ (10 mol%), and AgOAc (3 equiv.) in 4 mL of anhydrous CH_3CN at 80 °C for 48 h under CO in freshly distilled CH_3CN. [b] Isolated yields.

Ar_2 ring underwent the expected oxidative carbonylation reaction regioselectively to generate benzopyranones **2b–d**, respectively, in 70–87% yields (Table 2, entries 2–4). This reaction was also applied to substrates **1** with a chloro substituent on Ar_2 (entry 5) and heterocycles such as 2-furyl and 2-thienyl on Ar_2 (entries 6 and 7). In addition, benzopyranone **2h** with a 3,4-methylenedioxy moiety can be prepared in 68% yield (entry 8). Compound **2h** was prepared previously in five steps from D-ribose.[20] Our interest in understanding the chemical reactivity of **1** with other EDG or EWG groups on the Ar_1 ring prompts us to prepare substrates **1i–v**. The examples with an electron-withdrawing fluoro group at the 3 (entries 9–12) or the 4 (entries 13–16) position of Ar_1 all underwent oxidative CO insertion to give **2i–p** in 65–87% yields. This indicated that a fluoro group on Ar_1 does not influence the chemical reactivity for CO insertion. We then found that substrates **1q–r** with a chloro moiety at the 4 position of Ar_1 also reacted smoothly with CO to give the expected products **2q–r**, respectively, in 75–85% yields (entries 17 and 18). It is worthwhile to point out that the present C–H activation–carbonylation is not compatible with substrates equipped with a methyl group on Ar_1—no desired CO insertion spots were observed by TLC analysis (entries 19 and 20). The benzylic C–H bonds of these substrates could be easily activated followed by CO insertion and reductive elimination with another 2-arylphenol to give esters. Repetitiously the intermolecular process will give polymeric species. The present catalytic reaction was applicable to substrates with Ar_2 of the 2-naphthyl moiety to give substituted 6*H*-naphtho[2,3-*c*]chromen-6-ones in good yields regioselectively (entries 21 and 22). Furthermore, the reaction of 1-phenylnaphthalene-2-ol (**1w**) with CO proceeded effectively to give **2w** in 75% yield (entry 23). Finally, difluoro-substituted 2-arylphenols did not produce the expected CO insertion products likely due to the instability of the intermediates having more electron-withdrawing groups on the phenol ring in the catalytic process (entries 24 and 25).

In conclusion, we have demonstrated an efficient Pd-catalyzed oxidative carbonylation of 2-arylphenols *via* one O–H and C–H bond cleavage, and one new C–C and C–O bond formation under mild conditions with tolerance of a variety of substrates in good yields.

We thank the National Science Council of Taiwan, NCTU and NTHU for financial support of this research.

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